The Liver in Oncology

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KEYWORDS

• Drug-induced liver injury • Venooclusive liver disease
• Sinusoidal obstruction syndrome • Nodular regenerative hyperplasia
• Autoimmune hepatitis • Radiation toxicity • Hepatitis B reactivation

KEY POINTS

- Clinicians will often encounter oncologic patients with elevated liver tests or hepatic imaging abnormalities.
- Oncologic agents can cause hepatotoxicity by direct toxicity, idiosyncratic reactions, and immune-mediated hepatotoxicity.
- Those undergoing hematopoietic stem cell transplantation with preexisitng liver disease or receive certain oncologic agents are at high risk for venoocclusive disease.
- A late complication of chemotherapy can be nodular regenerative hyperplasia, with an insidious onset.
- All patients receiving chemotherapy should be screened for hepatitis B; reactivation should be considered in any patient receiving chemotherapy who presents with abnormal liver tests.

INTRODUCTION

Over the past 20 years, those who are diagnosed with solid and hematologic cancers have had an increasing number of therapeutic options to treat their malignancies. And many of these patients are experiencing improved overall survival and long-term remissions with the introduction of new classes of oncologic agents including new cytotoxic agents, targeted therapies, and immunooncologic agents. However, these new agents and combinations of agents have come with additional toxicities and, given that the liver is responsible for the metabolism of the majority of oncologic agents, hepatotoxicity may occur while receiving adjuvant therapy for a variety of solid and hematologic malignancies. Unrelated to direct hepatotoxic effects of chemotherapy to the liver, viral infections such as hepatitis B may reactivate in those who have active infection (hepatitis B surface antigen [HBsAg] positive), including those who have

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cleared HBsAg.[1] The liver is also more commonly involved as an organ to which metastases spread than any other organ, including the lung, with 50% of patients with a primary malignancy developing hepatic metastases. Radiation therapy and other locoregional therapies may be used to treat metastatic lesions to the liver in addition to chemotherapy and resection. In this review, we discuss common liver-related problems encountered by those who care for patients with oncologic disorders.

CHEMOTHERAPY-INDUCED DRUG-INDUCED LIVER INJURY

Classically, drug-induced liver injury has been described as either a result of a direct hepatotoxic effect on hepatocytes (such as acetaminophen) or an idiosyncratic effect that depends on a variety of factors, including host genetic factors.[2] In general, idiosyncratic reactions are more common than direct toxic reactions (such as acetaminophen). However, many chemotherapeutic agents and regimens are dosed based on the highest dose tolerated without toxicity; thus, in oncologic patients, clinicians must recognize that both direct toxic effects of chemotherapy as well as idiosyncratic reactions can cause hepatotoxicity. In addition, preexisting liver disease may also lead to a more severe hepatotoxic pattern. That is, those with normal liver chemistries and no liver disease typically tolerate chemotherapeutic regimens better than those with advanced fibrosis or cirrhosis.[3] The presence of common hepatic disorders such as nonalcoholic fatty liver disease does not seem to increase the incidence of drug-induced liver injury, although the severity of the hepatotoxic event may be higher in the setting of chronic liver disease, particularly advanced fibrosis. Thus, many oncologic agents require dose modifications for elevations in bilirubin, aminotransferase levels, and alkaline phosphatase levels. A useful categorization of those with abnormal liver tests who have received oncologic agents is the use of the R-value. The R-value is defined as alanine aminotransferase/upper limit of normal ÷ alkaline phosphatase/upper limit of normal. If the R-value is greater than 5, this implies hepatocellular injury; if the R-value is less than 2, this implies cholestatic injury; and if it is between 2 and 5, this implies a mixed hepatitic cholestatic pattern of injury.

Before we discuss chemotherapeutic agents that cause drug-induced liver injury, a brief review of classes of chemotherapy is in order. Cytotoxic chemotherapeutic agents may be broadly classified as alkylating agents, antimetabolites, mitotic inhibitors, and antibiotics,[4] other broad classes of chemotherapy include molecular targeted therapies and immunotherapies.

Patterns of Hepatotoxicity-Associated Oncologic Classes of Drugs

Alkylating agents

Alkylating agents are a classic group of chemotherapeutic agents that binds to DNA to prevent DNA replication. Alkylating agents are used to treat a variety of solid tumors as well as hematologic malignancies, and are generally classified as nitrogen mustards, nitrosoureas, alkyl sulfonates, triazines, and ethylenimines. As a group, the alkylating agents have low rates of hepatotoxicity with only rare reports of cholestatic hepatitis with temozolomide,[5] cyclophosphamide,[6] and chlorambucil (**Table 1**).[7]

Antimetabolites

Antimetabolites interfere with DNA replication and cell division by causing cell death when incorporated into DNA or RNA. Antimetabolites are used in the treatment of hematologic malignancies and solid tumors, including acute myelogenous leukemia, breast cancer, head and neck cancers, and gastrointestinal cancers. Hepatotoxicity has been reported with several of the antimetabolites including 6-mercaptopurine, which is used in the treatment of acute lymphoblastic leukemia, and may cause a